REMARKS

Applicants gratefully acknowledge the personal interview granted by the Examiner on February 5, 1998. The claims have been amended in accordance with the issues discussed at the interview in the expectation that the amendments will place this application in condition for allowance.

Basis for the amendments to claims 1, 6, 7, 10, 29 and 37 may be found in the specification on page 5, lines 21-37, page 6, lines 1-16 and page 8, lines 10-32. Basis for the amendments to claims 8, 9, 34, 35, 43, and 44 may be found in the specification on page 18, lines 36-37 and page 19, lines 1-2. Basis for the amendment to claim 21 may be found in the specification on page 4, lines 25-31.

Applicants submit that the amendments do not introduce new matter within the meaning of 35 U.S.C. § 132. Accordingly, entry of the amendments is respectfully requested.

1. Restriction Requirement

The Examiner has required restriction of claims 1-44 to one of the following inventions under 35 U.S.C. § 121:

I. Claims 1-9, drawn to a stable, sterile gelled composition, classified in Class 424, subclass 484+.

II. Claims 10-28, drawn to a method for the treatment of a condition, classified in Class 424, subclass 484+.

III. Claims 29-36, drawn to an antiarthritic gelled composition, classified in Class 424, subclass 484+.

IV. Claims 37-44, drawn to a method for treating an arthritic condition, classified in Class 514, subclass 825.

As the basis for the Restriction Requirement, the Office Action states:

> Inventions Group I and Group III are related as mutually exclusive species in intermediate-final product relationship. Distinctness is proven for claims in this relationship if the intermediate product is useful to make other than the final product (M.P.E.P. § 806.04(b), 3rd paragraph), and the species are patentably distinct (M.P.E.P. § 806.04(h)).
>
> In the instant case, the intermediate product is deemed to be useful as a bone cell formation/stimulating substrate and the inventions are deemed patentably distinct since there is nothing on this record to show them to be obvious variants.
>
> Inventions Group III and Group IV are related as product and process of use. . . In the instant case the product as claimed can be used in a materially different process such as a method for treating an arthritic condition which comprises orally administering to an animal and/or mammal a NSAID drug dispersed within a polymer matrix.

A. Election

With respect to the restriction requirement, applicants provisionally elect claims 1-9, Group I, with traverse.

B. Traversal

Applicants respectfully traverse the Examiner's restriction requirement.

The restriction requirement is improper because it omits "an appropriate explanation" as to the existence of a "serious burden" if a restriction were not required. (M.P.E.P. § 803,

Revision 3, July 1997). An examination of all the claims in this application would not pose a serious burden because a search of any one of invention Groups I, II, III, and IV would require searching the prior art areas appropriate to the other invention Group.

Groups I, II, III and IV are directed to topical treatments for treating various conditions, with Groups III and IV merely being more specifically related to treating arthritic conditions with said topical treatments. Given their overlapping subject matter, examinations of all four invention Groups would not pose a serious burden because they would be coextensive.

Furthermore, it is important for the Examiner to understand that applicants have paid a filing fee for an examination of all the claims in this application. If the Examiner refuses to examine the claims paid for when this application was filed, applicants must pay duplicative fees to file a divisional application for the non-elected or withdrawn claims.

Additionally, topical treatments for use in the treatment of any appropriate condition would certainly be within the same classes and subclasses. Therefore, there would be no substantial burden on the Examiner to search all of the disclosed species.

In view of the foregoing, applicants respectfully request that the Examiner reconsider and withdraw the restriction requirement and allow all claims pending in this application.

2. Rejection of Claims 1-44 under 35 U.S.C. § 112, 2nd Paragraph

The Office Action states that claims 1-44 are rejected under 35 U.S.C. § 112, second paragraph for the following reasons:

> In claims 1, 13, 14, 15, 24, 25 and 26, the term "mean" renders the claim vague and indefinite since mean ordinarily means average which applicants have already recited in each of the noted claims. Moreover, "average molecular weight" is vague and indefinite since for high polymers such descriptive language renders the claim indefinite absent an indication on how the average molecular weight was determined such as by number average molecular weight, weight average molecular weight and the like.
>
> In claims 2 and 38, the term "derivatives" renders each of the noted claims vague and indefinite. It is not clear from this disclosure whether applicants intend chemical derivatives or mechanically modified derivatives. Furthermore or in any event, derivatives would read on any molecular fragment of the parent molecule referred to and thus it is impossible to determine the subject matter covered by each of the noted claims.
>
> In claims 6 and 7, the use of the term "polymers" lacks clear antecedent basis in claim 1 in each instance. This is because applicants use the open transitional "comprises" and thus allows (sic) for the presence of other (sic) polymers other than those specifically enumerated in claim 1.
>
> In claim 8, it is not clear what the weight percents are based on. The same holds true for claim 9, claim 15, claim 1, claim 26, claim 29, claim 34, claim 35, claim 43 and claim 44.
>
> In each of the dependent claims from claim 37 which recite a polymer, each polymer lacks clear antecedent basis in claim 37 since claim 37 sets forth plural polymers blended with plural polymers.
>
> Claim 21 provides for the use of a composition as a medical device, for drug delivery, the application of a diagnostic agent, or the prevention of post-operative adhesions, but, since the claim does not set forth any

> steps involved in the method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

With regard to a § 112, second paragraph rejection, case law has defined two requirements under the statute: (1) that the applicant states the invention as something elsewhere in the application which would fall within the scope of the claims; and (2) that the claims are communicated with a reasonable degree of particularity and distinctness to a person skilled in the art in light of the content of the disclosure and the teachings of the prior art. MPEP § 2171, § 2173, and § 2173.02.

Applicants submit that the foregoing amendments to claims 1, 6-10, 13-15, 21, 24-26, 29, 34, 35, 37, 43 and 44, obviate this rejection. Further, claims 2 and 38 have been canceled, thus obviating the rejection based thereon.

Claims 13-15 and 24-26 have been amended to remove the terminology "mean" to remedy the redundancy noted by the Examiner. Applicants submit that the term "average molecular weight" is not indefinite because a number average molecular weight is always implied in the absence of any indication to the contrary (i.e., the molecular weight is the sum of the atomic weights of the atoms in a molecule and as such is not generally given in units).

Claims 1, 8, 9, 29, 34, 35, 43 and 44 have been amended to add the terminology "of the resulting composition", to clarify that the percentages in the claims are based on the percent by weight of the

final delivery system or formulation prepared. (Specification, page 18, lines 36-37 and page 19, lines 1-2).

Claim 21 has been amended to clarify the steps of the claimed process and remove the alleged indefiniteness. Applicants submit that the claim, as amended, is a valid process claim and thus the alleged indefiniteness is cured by the amendment.

Claims 6 and 7 have been amended to add the terminology "negative charged polymer to the nonionic polymer" to clarify which polymers of claim 1 are referred to and thus cure the alleged lack of antecedent basis.

Accordingly, the claims, as amended, do reasonably apprise persons of ordinary skill in the art of the invention's scope. Therefore, applicants respectfully request that the Examiner reconsider and withdraw the rejections.

3. Rejection of Claims 21-28 under 35 U.S.C. § 101

The Office Action states that claims 21-28, are rejected under 35 U.S.C. § 101. As the basis of this rejection, the Office Action states:

> . . . the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. § 101.

Section 101 of Title 35 states the scope of eligibility for a utility patent, as follows: "Whoever invents or discovers any new

and useful process, machine, manufacture, or composition of mater, or any new and useful improvement thereof, may obtain a patent therefor . . . A "process" is broadly defined as a "process, art or method". 35 U.S.C. § 100(b).

Applicants submit that the amendment to claim 21 obviates the Examiner's rejection. Claim 21 has been amended to recite the two step process which would be required to achieve the desired result. Further, each step of the claimed process is sufficiently described in the specification to enable one skilled in the art to practice the invention. Therefore, applicants respectfully request the Examiner to reconsider and withdraw the rejection.

4. Rejection of Claims 1-44 under 35 U.S.C. § 103

The Office Action states that claims 1-44, are rejected under 35 U.S.C. § 103, as being obvious over Leshchiner et al.

As the basis of this rejection, the Office Action states:

> Leshchiner et al. disclose biocompatible viscoelastic two-phase gel slurries wherein the first phase comprises hyaluronic acid and its salts (see column 3, lines 59-62). The second phase comprises cellulose derivatives such as carboxymethyl cellulose (CMC), hydroxypropylmethyl cellulose and hydroxyethyl cellulose (see column 4, lines 45-50). The solvent can be water. The concentration of hyaluronic acid can be from 0.15-5% by weight (see column 6, lines 61-64). The compositions may contain drugs (see column 7, lines 60-65). Example 12 shows a composition comprising a 1:1 CMC-hylan gel (see column 18, lines 31-37). It would have been within the purview of one having ordinary skill in the art at the time the invention was made to select the claimed active given the clear suggestion of a generic teaching of any drug which can be used in the gels of Leshchiner

> et al. and thus absent a showing of superior results in a particular drug, all drugs disclosed usable in the gels are viewed as equivalent for the purposes of Leshchiner et al.

Applicants respectfully traverse and submit that the amendments to claims 1, 10, 21 and 29 obviate the rejection. The reference of record, Leshchiner et al., does not teach or suggest applicants' inventive subject matter as a whole as recited in the amended claims. It is not even apparent what would lead the ordinary skilled artisan to modify the disclosure of Leshchiner et al. to derive the subject matter claimed by applicants.

The U.S. Supreme Court in *Graham v. John Deere Co.*, 148 U.S.P.Q. 459 (1966) held that non-obviousness was determined under § 103 by (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and, (4) inquiring as to any objective evidence of nonobviousness.

A. The present inventive subject matter

Applicants' claims as presently amended are directed to a stable, gelled, polymer matrix capable of holding a therapeutic drug suspended in the matrix and allowing sustained release of the therapeutic drug for prolonged periods of time. The inventive subject matter is further directed toward compositions which may be applied topically and which exhibit transdermal characteristics. Specifically, the compositions allow for sustained release of a therapeutic drug across the dermal barrier.

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The present inventive subject matter incorporates a polymer matrix consisting of negatively charged polymers and nonionic polymers combined in approximately equal amounts. This system is designed to administer effective levels of drugs for a prolonged period of time. To achieve the desired sustained release, it is extremely important for there to be a suitable ratio between the negatively charged polymer(s) and the nonionic polymer(s) in the polymer matrix. (Specification, page 5, lines 21-31).

A new and unexpected aspect of the inventive subject matter is the ability to achieve a storage stable gel capable of sustained release of a therapeutic drug by employing compositions with a relatively equal ratio of negatively charged polymer(s) to nonionic polymer(s). It has been found that compositions with molar ratios outside the claimed boundaries develop various defects, such as air pockets and separation of the polymers, compromising the stability of the compositions and inhibiting their ability to sustain a long acting release of a therapeutic drug. (Specification, page 5, lines 25-31). It has also been unexpectedly discovered that the use of a negatively charged polymer is critical to aid in the dispersion of the drug throughout the matrix, further prolonging and controlling the release (Specification, page 5, lines 32-34).

B. The prior art

Leshchiner et al. disclose biocompatible viscoelastic gel slurries consisting of two phases. More specifically, the slurry comprises a polymer in a liquid phase solvent, which may, or may not, be another polymer. Leshchiner et al. do not disclose stable, gelled compositions or any manner of achieving transdermal, sustained release drug delivery.

Leshchiner et al. teach a slurry which is able to form a suspension where the polymer does not dissolve in the liquid phase, but is uniformly dispersed (See column 2, lines 10-12). This covers a broad range of possible solvents. The solvent may or may not be a polymer, as long as it does not dissolve the polymer suspension or have an adverse reaction to living tissue. (See column 4, lines 29-60).

Leshchiner et al. also disclose the application of pressure on the gel to control the polymer concentration. (See column 6, lines 3-18). Leshchiner et al. teach that the controlling of polymer concentration in the gel phase, and hence equilibrium swelling are important functions of obtaining the desired slurry.

C. The differences between the claimed subject matter and the prior art

Applicants respectfully submit that the amendments to claims 1, 10, 21 and 29 obviate the Examiner's rejection and that the differences between applicants' inventive subject matter and the disclosure in Leshchiner et al. are startling and readily apparent

from the independent and distinct disclosures and claims. There are several distinctions to which applicants specifically direct the Examiner's attention.

First, applicants' compositions are unexpectedly capable of attaining transdermal drug delivery on a sustained release basis, while Leshchiner et al. do not even address transdermal sustained release drug delivery. Transdermal sustained release is attainable because of applicants' discovery that the polymer ratio ranges to which the inventive subject matter is limited will allow for same. By limiting the present invention to said polymer ratio ranges, the prior art compositions taught by Leshchiner et al. are nonobvious with regard to the particular purpose for which the compositions of the present invention are used (i.e., topical application for sustained release drug delivery).

Even if certain compositions disclosed by Leshchiner et al. were to overlap the polymer ratio ranges of the present inventive subject matter, the failure of Leshchiner et al. to recognize the significance of the ratio of negative charged polymers to nonionic polymers, for the purpose of the present invention, represents a nonobvious disclosure. It would not have been obvious to one of ordinary skill in the art to use the compositions disclosed by Leshchiner et al. to achieve a stable, gelled composition capable of transdermal sustained release drug delivery where the disclosure did not suggest that such a composition could be achieved.

Secondly, the present invention is limited to stable gels suitable for topical application. Stability is achieved through the presence of the negative charge limitation and the polymer ratio ranges to which the invention is limited. In contrast, Leshchiner et al. disclose compositions which would be unstable and exhibit the polymer shearing effect which produces unacceptable turbulence and air pockets in said compositions with resulting loss of potency and efficacy. (Specification, page 5, lines 25-31). Moreover, Leshchiner et al. teach a gel slurry where the polymer is suspended in an aqueous phase that may or may not be another polymer, whereas the applicants' inventive subject matter is specifically limited to a mixture of polymers and not a slurry (i.e., a thin watery suspension). The unstable slurries disclosed by Leshchiner et al. are not only absent in applicants' inventive subject matter, but would be completely inappropriate for the applicants' claimed inventive subject matter which requires a stable, gelled polymer mixture suitable for topical application.

Finally, the specific negatively charged polymers to which the amended claims are limited represent an essential element in achieving the dispersion of the drug throughout the polymer matrix. The even dispersion of drug throughout the polymer matrix is necessary for achieving an efficacious sustained release of drug. The disclosure of Leshchiner et al. is deficient in its failure to address the issue of achieving even dispersion of drug throughout a polymer composition.

In this regard, applicants' use of polymer matrixes are not disclosed or suggested by Leshchiner et al. By disclosing slurries not dependent on the molar ratio of negative charged to nonionic polymers, Leshchiner et al. fail to appreciate the unexpected properties of using equal mixtures of nonionic and negative charged polymers, as claimed by applicants. The fact that a claimed product is within the broad field of the prior art and one might arrive at it by selecting specific items and conditions does not render the product obvious in the absence of some directions or reasons for making such selection. Ex parte Kuhn, 132 USPQ 359 (POBA 1961). Leshchiner et al. do not recognize the advantageous properties of a polymer mixture which is not a two phase suspension, or the usefulness of a specific polymer mixture unexpectedly found to store and release therapeutic drugs efficiently, efficaciously and transdermally, over prolonged periods of time. In failing to appreciate their advantages, Leshchiner et al. provide no reason or incentive for using polymer matrixes as claimed by the applicants. Thus, not only does the patent fail to provide the present inventive subject matter, but the Leshchiner et al. patent teaches away from applicants' inventive subject matter.

It is readily apparent that there is no disclosure of facts in the prior art which support a legal conclusion that the claimed invention was obvious at the time it was made. It is a well settled principle that prior patents are references only for what

they clearly disclose or suggest and that it is not proper to use a patent as a reference when its structure is modified to one which the reference does not suggest.

It is readily apparent from the reference relied upon that the technology disclosed in our application is totally unrelated to that which is disclosed by this reference.

The provisions of Section 103 must be followed realistically to develop the factual background against which the Section 103 determination must be made. All of the facts must be considered and it is not realistic within the framework of Section 103 to pick and choose from any one reference only so much as will support a given position to the exclusion of other parts necessary for the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. Accordingly, withdrawal of the rejection and an allowance of claims 1, 3-10, 12-21, 23-37 and 39-44 is respectfully requested.

CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections of the remaining claims, and allow all pending claims presented herein for reconsideration. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcome to telephone the undersigned attorney if he has any questions or comments.

Respectfully submitted,

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Date: March 12, 1998

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